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| 10/816,081 | 04/01/2004 | David B. Rozema | Mirus.035.02.1 | 8619 |

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| EXAMINER | |
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| DUNSTON, JENNIFER ANN | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/816,081 | ROZEMA ET AL. | |
| | Examiner | Art Unit | |
| | Jennifer Dunston | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *19,22,23 and 27-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,22,23 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This action is in response to the amendment, filed 4/28/2009, in which claims 19, 22, 23, 27-29 and 32 were amended. Claims 19, 22, 23 and 27-32 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

### *Election/Restrictions*

Applicant elected Group II without traverse in the reply filed on 9/18/2006. Currently, claims 19, 22, 23 and 27-32 are under consideration.

### *Claim Objections*

Claim 27 is objected to because of the following informalities: the word "are" should be inserted between the words "disubstituted maleic anhydrides" and "selected from" to improve the grammar of the claim. Appropriate correction is required.

Claim 32 is objected to because of the following informalities: the phrase "wherein ternary" should be amended to recite "wherein said ternary" or "wherein the ternary" to improve the grammar of the claim. Appropriate correction is required.

### *Response to Arguments - 35 USC § 112*

The rejection of claim 32 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claim in the reply filed 4/28/2009.

***Response to Amendment – Declaration of David B. Rozema and Darren Wakefield***

The declaration under 37 CFR 1.132 filed 4/28/2009 is sufficient to overcome the rejection of claims 19, 23 and 27-29 based upon the application of the Rozema et al (2004/0156909) reference under 35 U.S.C. 102(e), and the rejection of claims 19, 23, 27 and 28 under 35 U.S.C. 102(e) based upon the application of the Lewis et al (2003/0224055) reference.

***Response to Arguments - 35 USC § 102***

The rejection of claims 19, 23 and 27-29 under U.S.C. 102(b) as being anticipated by Wolff (WO 00/75164 A1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/28/2009. Wolff does not teach the method where the polycation and the reversibly inhibited membrane active polymer are both amine-containing amphiphilic polyvinylether polymers.

Applicant's arguments, see page 4, filed 4/28/2009, with respect to the rejection of claims 19, 23 and 27-29 under 35 U.S.C. 102(e) as being anticipated by Rozema et al (2004/0156909) have been fully considered and are persuasive in view of the declaration under 37 C.F.R. 1.132. The previous rejection of claims 19, 23 and 27-29 has been withdrawn.

Applicant's arguments, see page 4, filed 4/28/2009, with respect to the rejection of claims 19, 23, 27 and 28 under 35 U.S.C. 102(e) as being anticipated by Lewis et al (2003/0224055) have been fully considered and are persuasive in view of the declaration under 37 C.F.R. 1.132. The previous rejection of claims 19, 23, 27 and 28 has been withdrawn.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 23 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference) in view of Goldenberg et al (US Patent No. 5,629,184; see the entire reference) and Pfohl et al (US patent No. 4,880,497; see the entire reference). This is a new rejection, necessitated by the amendment of the claims in the reply filed 4/28/2009.

Wolff exemplifies a method for delivering a polynucleotide to the cytoplasm of a cell, comprising (i) condensing the polynucleotide with a poly-L-lysine (PLL) polycation to form a binary complex; (ii) associating the binary complex with a reversibly inhibited membrane active polymer to form a ternary complex (recharging); and (iii) delivering the ternary complex to a cell, wherein the ternary complex is endocytosed by the cell (e.g., page 76, line 15 to page 78,

line 15; page 106, line 19 to page 107, line 15). Wolff teaches the method where the "reversibly inhibited membrane active polymer" is a membrane active polyamine selected from the group consisting of melittin, $KL_3$, $KL_3PLL$ to which a plurality of disubstituted maleic anhydride derivatives are reversibly linked via pH labile bonds (e.g., paragraph bridging pages 52-53; page 76, line 15 to page 78, line 15). Further, Wolff teaches that linkage of the disubstituted maleic anhydride derivatives to the membrane polyamine polymer inhibits liposome leakage activity (as measured by red blood cell lysis) of the membrane active polyamine and cleavage of the disubstituted maleic anhydride derivatives from the reversibly inhibited membrane active polymer restores liposome leakage activity of the membrane active polyamine (e.g., paragraph bridging pages 21-22; page 24, line 5 to page 25, line 4; paragraph bridging pages 52-53; page 103, line 25 to page 104, line 12). Thus, Wolff teaches the method where (a) a first amine-containing polymer is formed; (b) a second amine-containing polymer capable of causing liposomal leakage is formed; (c) the second amine-containing polymer is modified via covalent linkage of a plurality of disubstituted maleic anhydride derivatives, where the disubstituted maleic anhydride derivatives inhibit the membrane active polymer until the maleic anhydride derivatives are cleaved off the polymer in the acidic endosome; (d) the first amine-containing polymer is complexed with a polynucleotide to form a binary complex; (e) the binary complex is associated with the reversibly inhibited membrane active polymer to form a ternary complex; and (f) a cell is contacted with the ternary complex resulting in the delivery of the polynucleotide to the cell (see the discussion above and page 20, line 28 to page 22, line 4; page 38, lines 7-27). Wolff teaches that the polymers of the invention can be produced by step polymerization or chain polymerization (e.g., page 39, line 18 to page 42, line 9). For chain polymerization, Wolff

teaches the use of monomers containing vinyl groups (e.g., page 41, lines 28-33). Wolff teaches the method where the membrane active polyamine disrupts an endocytic membrane after cleavage of the disubstituted maleic anhydride moiety thereby providing delivery of the polynucleotide to the cytoplasm of the cell (e.g., paragraph bridging pages 52-53; page 76, line 15 to page 78, line 15; page 106, line 19 to page 107, line 15). Wolff teaches the method where the disubstituted maleic anhydride derivatives are carboxydimethylmaleic anhydride (2-propionic-3-methylmaleic anhydride) (e.g., paragraph and bridging pages 52-53; page 64, lines 1-18; page 66, lines 22-27; page 77, line 22 to page 78, line -15). Wolff teaches the method where the disubstituted maleic anhydride derivatives are cleaved from the polyamine in an endosome (e.g., paragraph bridging pages 52-53; page 76, line 15 to page 78, line 15; page 106, line 19 to page 107, line 15).

Wolff does not teach the method where the first and second amine-containing polymers are amine-containing amphiphilic polyvinylether polymers.

Goldenberg et al teach the cytoplasmic delivery of polyanions, such as oligonucleotides, based on studies in which copolymers based on vinyl alcohol and vinyl amine (PVAVAMs) were used to deliver the oligonucleotides to the cells (e.g., paragraph bridging columns 2-3). Goldenberg et al teach that the PVAVAMs are prepared using hydrophobic and hydrophilic polymerizable vinylic monomers that have from 0.5-75 mole % vinyl amine content (e.g., column 3, lines 19-27). Although Goldenberg et al exemplify the use of vinyl alcohol/vinyl amine polymers (e.g., Example 2), Goldenberg et al teach that one skilled in the art would recognize variations in the method of preparation of the polymers, including the use of vinyl alkyl ethers, wherein the alkyl portion has 1 to 6 carbon atoms (e.g., column 4, lines 14-25).

Further, Goldenberg et al teach that the copolymers may be modified by maleic anhydride (e.g., column 4, lines 55-63). Goldenberg et al teach that there have been extensive reports on the synthesis of the copolymers, including US Patent No. 4,880,497 (e.g., column 2, lines 43-51).

Pfohl et al teach the production of water-soluble copolymers containing copolymerized vinylamine units, where the copolymers are prepared by copolymerizing (a) from 95 to 10 mol% of N-vinylformamide and (b) from 5 to 90 mol % of an ethylenically unsaturated monomer such as $C_1$ to $C_4$ alkyl vinyl ethers, and hydrolyzing the formyl group to produce polyamine polymers with a molecular weight greater than 10000 Da (e.g., Abstract; column 1, line 58 to column 3, line 38; column 4; Examples 1-2).

Because Wolff teaches the use of amine-containing polymers for the delivery of a polynucleotide to a cell and suggests the use of polymers composed of vinyl monomers, and Goldenberg et al teach copolymers comprising an alkyl vinyl ether and vinyl amine monomers for the delivery of a polynucleotide to a cell, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the polyamine polymer of Wolff (e.g., poly-L-lysine) with vinyl ether/vinyl amine copolymer of Goldenberg et al in order to achieve the predictable result of providing a polycationic polyamine polymer for condensation of DNA in a binary complex and for providing a polymer that is modified to contain membrane active moieties and is reversibly inhibited by carboxydimethylmaleic anhydride to recharge the binary complex for delivery of the polynucleotide to a cell. Furthermore, it would have been obvious to one of ordinary skill in the art to use polymers each having a molecular weight greater than 10,000 Daltons, because Goldenberg et al teach that methods of producing the polymers were

known in the art, and the prior art methods result in the production of polymers greater than 10,000 Daltons.

Claims 22 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference) in view of Goldenberg et al (US Patent No. 5,629,184; see the entire reference) and Pfohl et al (US patent No. 4,880,497; see the entire reference) as applied to claims 19, 23 and 27-29 above, and further in view of Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of the claims in the reply filed 4/28/2009.

The combined teachings of Wolff (WO 00/75164 A1), Goldenberg et al, and Pfohl et al are described above and applied as before. Further, Wolff teaches that DNA/polycation complexes can be recharged with a polyanion and crosslinked (e.g., page 13, lines 15-17; page 36, lines 9-17). Wolff teaches that particle formation should be reversible to allow escape of DNA from the endosome, and conditions that cause the reverse of particle formation may be the pH (e.g., page 10, lines 22-29). Wolff teaches the use of pH-labile bonds to allow reversal under lower pH conditions of the endosome (e.g., page 19, lines 25-30; page 22, line 32 to page 23, line 25; page 37, lines 1-14). Wolff teaches that disulfide bonds are inherently labile and can be used to construct very pH-labile bonds (e.g., page 48, lines 23-26). Further, Wolff teaches that it is preferable to use DNA complexes of about 100 nm (e.g., page 8, lines 5-17). Moreover, Wolff teaches that PEG chains act as a steric stabilizer that prevents aggregation of final polymer by sterically hindering particle to particle electrostatic interactions (e.g., page 44, lines 9-14). Wolff teaches the covalent attachment of PEG to 2-propionic-3-methylmaleic anhydride

(carboxydimethylmaleic anhydride, CDM) (e.g., page 66, lines 10-20), and the reaction of CDM-PEG with PLL (e.g., page 107, lines 26-29).

Wolff (WO 00/75164 A1), Goldenberg et al, and Pfohl et al do not specifically teach the method where the first amine-containing amphiphilic polyvinylether polymer is crosslinked to the reversibly inhibited membrane active polymer via a pH-labile bond to form a negatively charged, salt stable nanoparticle.

Wolff (WO 00/03694 A1) teaches the formation of condensed DNA with a polycation to form a binary complex, which is recharged with a polyanion (e.g., paragraph bridging pages 17-18). Wolff teaches that the binary complex of DNA and polycation can be recharged with a polyanion to provide the ternary complex with a net negative charge (e.g., paragraph bridging pages 17-18). Further, Wolff teaches that the interaction between the polycation and polyanion of the ternary complex may be via a covalent crosslink between cationic and anionic sites, including cleavable crosslinking systems, including those containing disulfide bonds (e.g., paragraph bridging pages 17-18). With regard to particle size of ternary complexes, Wolff teaches that a DNA/PLL binary complex recharged with succinic anhydride has a net negative charge and forms nanoparticles (e.g., page 18, lines 9-16; page 27, line 3 to page 28, line 8). When the cationic and anionic layers of the DNA particles were crosslinked, the stability of the nanoparticles was substantially improved (e.g., page 27, lines 9-11; Table 2). Furthermore, binary complexes of DNA and PLL recharged with PEG-SPLL displayed higher stability as compared to non-pegylated particles (e.g., page 28, lines 10-25; Table 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide to the cytoplasm of a cell of

Wolff (WO 00/75164 A1), Goldenberg et al and Pfohl et al to include the cross-linking of the polycation of the binary complex with the polyanion used to recharge the binary complex and form a ternary complex as taught by Wolff (WO 00/03694 A1) because Wolff (WO 00/75164 A1) teach it is within the ordinary skill in the art to use a recharging process to form a ternary complex and Wolff (WO 00/03694 A1) teach covalent linking of the polyanion used to recharge the binary complex containing the polycation. Furthermore, Wolf (WO 00/03694 A1) teaches the use of labile linkages in the crosslink, such as those containing a disulfide bond, and Wolff (WO 00/75164 A1) teaches very pH-labile bonds comprising a disulfide bond. Moreover, both Wolff references teach the addition of PEG to stabilize the complex, and Wolff (WO 00/03694 A1) teaches that pegylation stabilizes the particle while maintaining a small nanoparticle of about 100 nm, and Wolff (WO 00/75164 A1) teaches that particles of about that size are desirable.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a more stable nanoparticle as taught by Wolff (WO 00/03694 A1). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

***Response to Arguments - 35 USC § 103***

The rejection of claims 22 and 30-32 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/75164 A1) in view of Wolff (WO 00/03694 A1) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/28/2009. Wolff does not teach the

method where the polycation and reversibly inhibited membrane active polymer are both amine-containing amphiphilic polyvinylether polymers.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston
Examiner
Art Unit 1636

/JD/

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636